UT Southwestern
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Ophthalmology

Optic Neuritis and Optic Neuropathies: Beyond Multiple Sclerosis

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Conflict of Interest Disclosures

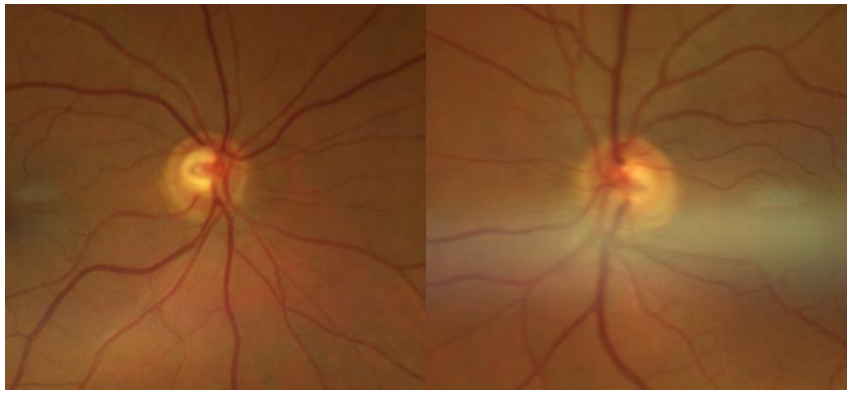
- I have no financial interests to disclose
- Principal Investigator: PIONEER-1 clinical trial for acute optic neuritis
- Sub-PI: TIMELY-PLEX clinical trial for severe optic neuritis

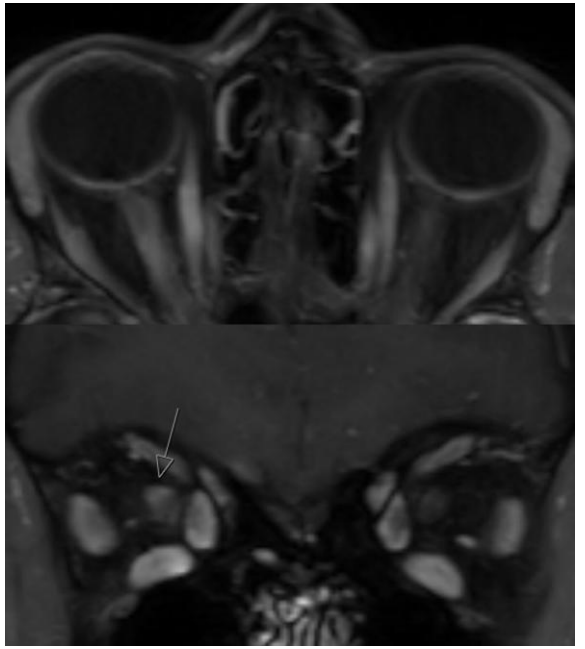
Learning Objectives

1) Recognize typical and atypical features of optic neuritis
2) Differentiate the etiologies for optic neuritis, including MOGAD and NMOSD
3) Identify ischemic, infectious, and hereditary optic neuropathies
4) Apply a systematic approach to optic neuropathy and disc swelling

A Familiar Presentation

- 28F acute, R blurry vision
  - Progressive over 3 days
  - Pain when she looks around
  - Exam
    - Visual acuities 20/30; 20/20
    - R rAPD, R dyschromatopsia
    - Non-specific VF defects
    - No disc changes appreciated
  - MRI brain w/wo





Diagnosis???

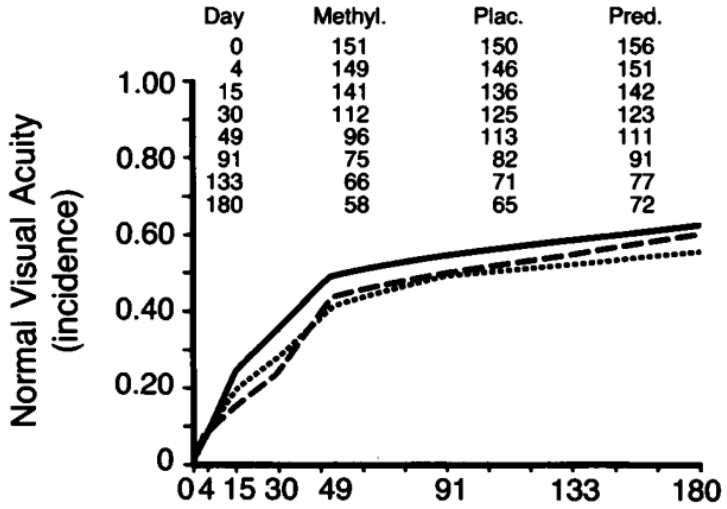
Typical MS Optic Neuritis: What Should We Expect?

	Typical Presentation
Age	Young adults (mean, 32yrs, F ~77%)
Onset	Acute/subacute
Laterality	Usually unilateral
Pain	92% ocular, 87% w/ eye movements
Optic disc	Normal (65%), swelling (35%)
Visual Function	Reduced acuity (severe ~33%), dyschromatopsia, contrast sensitivity loss, visual field defects, rAPD

Optic Neuritis Study Group. Arch Ophthalmol. 1991;109(12):1673–1678; Trobe JD, *et al.* Am J Ophthalmol. 1996;121:547–553; Chen JJ, *et al.* JAMA Ophthalmology. 2018;136(4):419–422; Bennett JL, *et al.* Lancet Neurol. 2023;22(1):89–100.

Lessons From Optic Neuritis Treatment Trial

- **Visual recovery**
  - Most experience substantial spontaneous visual improvement, typically within weeks
- **Corticosteroid treatment**
  - IV steroids accelerate visual recovery, do not significantly improve long-term visual acuity
- **Risk of developing MS**
  - Baseline brain MRI lesions are a major predictor of subsequent MS development



Adapted from Beck RW, *et al*. N Engl J Med. 1992;326(9):581–588. Figure 1.

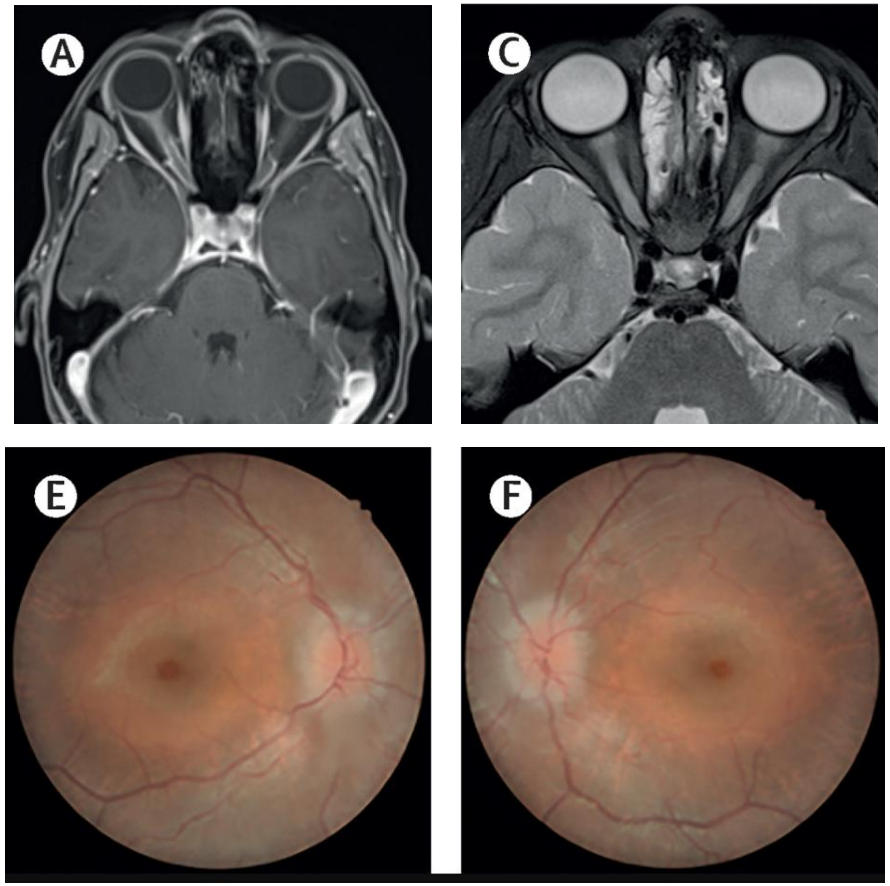
When Should We Question the Diagnosis of MS Optic Neuritis?

	Clinical Red Flags
Presentation	▪ Bilateral simultaneous vision loss; absence of pain
Optic disc/retina	▪ Severe disc edema; hemorrhages, exudates, or evidence of retinitis
Clinical course	▪ Visual deterioration beyond 2 weeks; lack of meaningful recovery; steroid dependence
MRI	▪ Longitudinally extensive optic nerve involvement; chiasmal or perineural enhancement
Associated findings	▪ Fever, systemic inflammatory symptoms, or other neurological abnormalities

Petzold A, *et al*. Lancet Neurol. 2022;21(12):1120–1134; Benard-Seguin E, Costello F. Ann Indian Acad Neurol. 2022;25(Suppl 2):S48–S53.

MOGAD: When Optic Neuritis Looks Different

- **Presentation:** Frequently severe vision loss; bilateral more common vs MS-ON
- **Optic disc:** Prominent edema, sometimes peripapillary hemorrhages
- **MRI:** Longitudinally extensive lesions, often anterior; perineural enhancement may occur
- **Treatment response:** Steroid responsive, possible relapse during taper/after withdrawal
- **Visual prognosis:** Often substantial recovery, despite severe vision loss at presentation

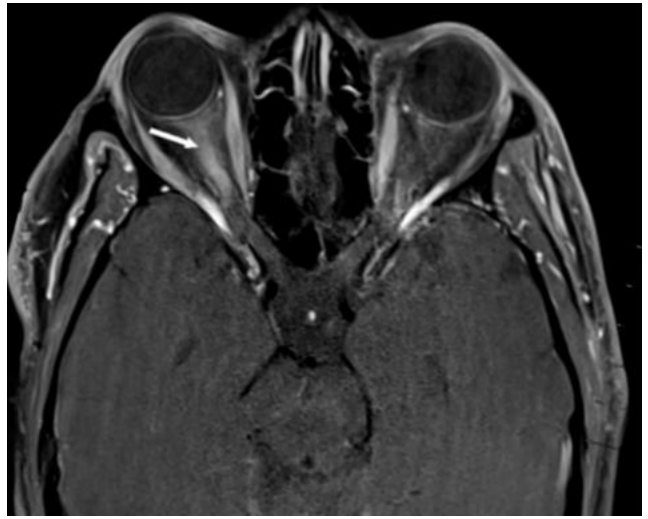


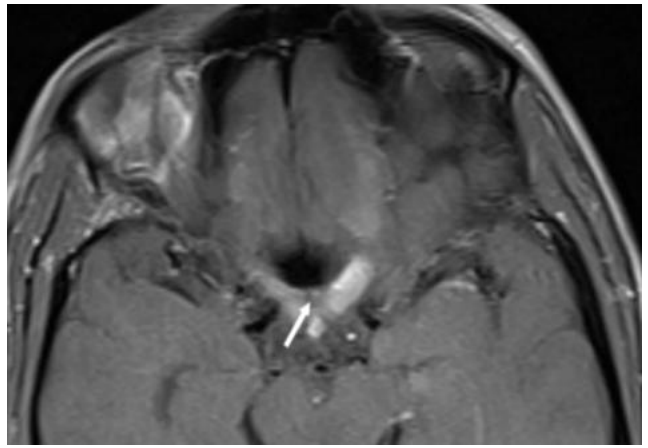
Adapted from Banwell *et al*., Lancet Neurol. 2023; Figure 2.

Banwell B, *et al.* Lancet Neurol. 2023;22(3):268–282.; Bergeron E, Bouffard MA. Curr Opin Ophthalmol. 2024;35(1):73–82.

AQP4-Neuromyelitis Optica Spectrum Disorder (NMOSD)

- **Presentation:** Often severe visual loss; unilateral or bilateral
- **Optic disc:** Often normal; possible edema but generally less prominent than in MOGAD
- **MRI:** Longitudinally extensive lesions, often posterior; optic chiasm involvement
- **Clinical course:** Severe attacks with potentially incomplete recovery
- **Visual prognosis:** Greater risk of permanent visual disability than MS-ON or MOGAD-ON





Adapted from Al Abdulghani and Galetta, Sclerosis. 2026; Figure 1.

Jarius S, *et al.* J Neurol. 2023;270:3341–3368; Moheb N, Chen JJ. Eye (Lond). 2023;37:2678–2690; Al Abdulghani A, Galetta SL. Sclerosis. 2026;4(3):24.

MS vs MOGAD vs AQP4-NMOSD: Three Phenotypes

	MS-ON	MOGAD-ON	AQP4/NMOSD-ON
Laterality	▪ Usually unilateral	▪ Unilateral or bilateral (more common)	▪ Unilateral or bilateral
Disc edema	▪ Absent or mild	▪ Often prominent	▪ Variable; less common than MOGAD
MRI pattern	▪ Shorter, often unilateral lesions	▪ Longitudinally extensive, often anterior; perineural enhancement	▪ Longitudinally extensive, often posterior; chiasmal involvement
Visual recovery	▪ Usually favorable	▪ Often favorable despite severe initial loss	▪ Frequently incomplete; greater risk of permanent impairment

Petzold A, *et al.* Lancet Neurol. 2022;21(12):1120–1134; Banwell B, *et al.* Lancet Neurol. 2023;22(3):268–282. Jarius S, *et al.* J Neurol. 2023;270:3341–3368.

Beyond Steroids: Improving Visual Outcomes in Optic Neuritis

Clinical Question	Clinical Trial
▪ Can we improve visual recovery after acute optic neuritis?	▪ PIONEER-1
▪ Can earlier plasma exchange improve visual outcomes in severe optic neuritis?	▪ TIMELY-PLEX

ClinicalTrials.gov. PIONEER-1. NCT07623668.; ClinicalTrials.gov. TIMELY-PLEX. NCT07100990.

Autoimmune and Paraneoplastic Optic Neuropathies: CRMP5 and GFAP

	CRMP5-associated	GFAP astrocytopathy
Clinical setting	▪ Paraneoplastic; think small-cell lung cancer	▪ Autoimmune meningoencephalomyelitis
Ocular phenotypes	▪ Often bilateral disc edema; vitritis/retinitis may coexist	▪ Disc edema, often bilateral; visual dysfunction variable
Key clues	▪ Intraocular inflammation, malignancy	▪ Headache, encephalopathy, myelitis, inflammatory CSF
Diagnostic approach	▪ CRMP5-IgG testing and directed malignancy evaluation	▪ CSF GFAP-IgG testing; correlate with clinical/MRI findings

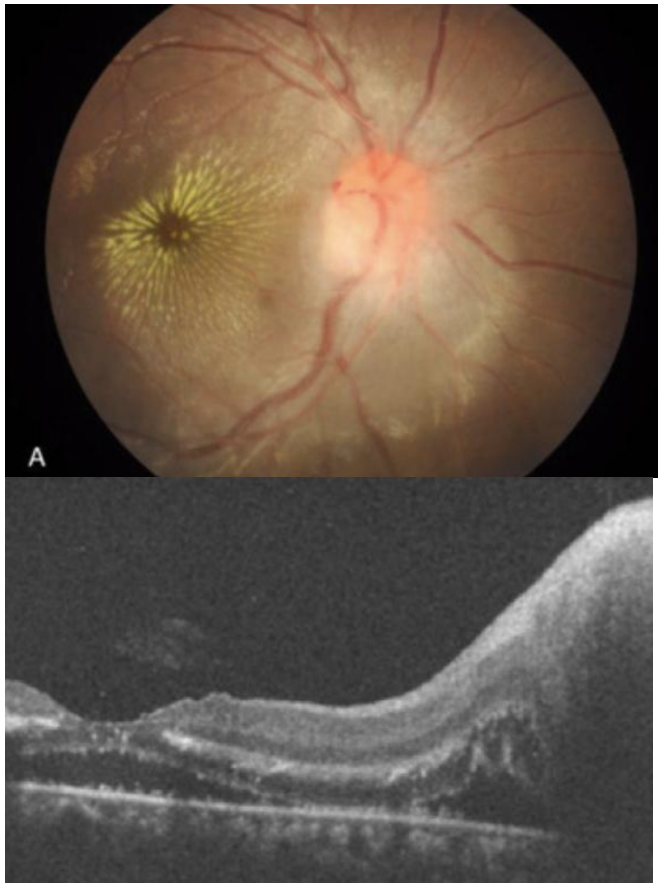
Bennett JL, *et al.* Lancet Neurol. 2023;22(1):89–100.; Yan Y, *et al.* Front Neurol. 2023;14:1172035.

Not All Is Demyelinating: Recognizing Neuroretinitis

- **Presentation:** Acute/subacute, typically painless unilateral visual loss
- **Optic disc:** Prominent edema, sometimes peripapillary hemorrhages
- **Macula:** Subretinal fluid; macular star may develop after 1–2 weeks
- **Etiologies:** Infectious (*Bartonella h.,* TB, syphilis, lyme), inflammatory (sarcoid), autoimmune (MOGAD)
- **MRI:** Often normal, may show focal optic disc enhancement
- **Treatment:** Etiology-directed; (e.g. doxycycline, +/- rifampin); steroids controversial

Clinical Pearl 1: Absence of macular star does not exclude

Clinical Pearl 2: Hypertensive retinopathy/malignant HTN can mimic



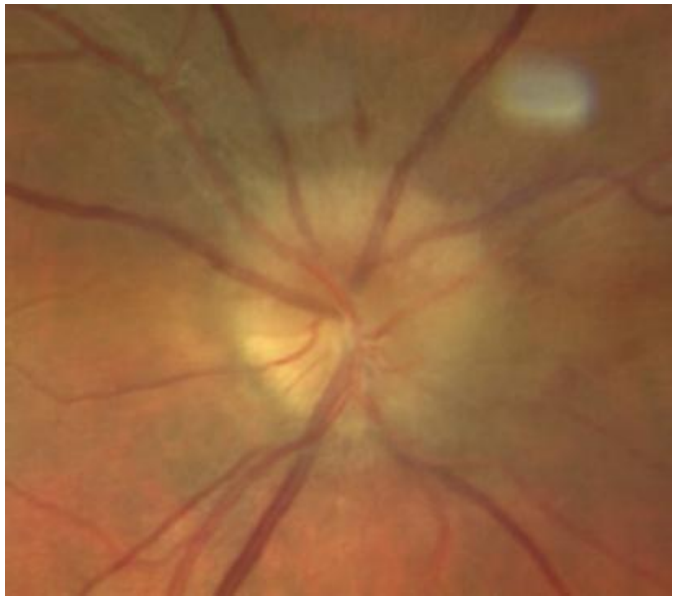
Adapted from Tey *et al.*, J Ophthalmic Inflamm Infect. 2020; Figure 2.

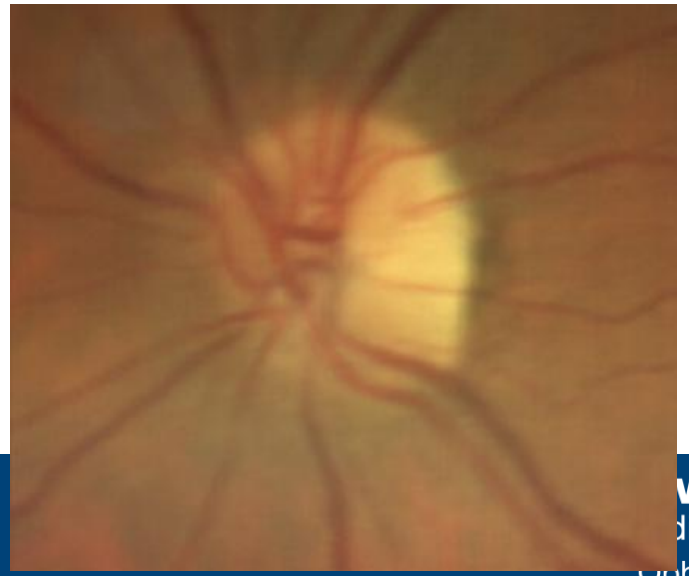
Shi J, *et al.* Eye (Lond). 2025;39:238–250.; Tey MSY, *et al.* J Ophthalmic Inflamm Infect. 2020;10(1):31.

Sudden Vision Loss: Is It Really Optic Neuritis?

- 62M presents with:
  - Sudden, painless, monocular vision loss upon awakening
  - PMH: HTN, DM2, OSA
  - Exam
    - rAPD
    - Acuity
    - Altitudinal VF defect
    - Sectoral disc edema w/ peripapillary hemorrhage; small cup fellow eye

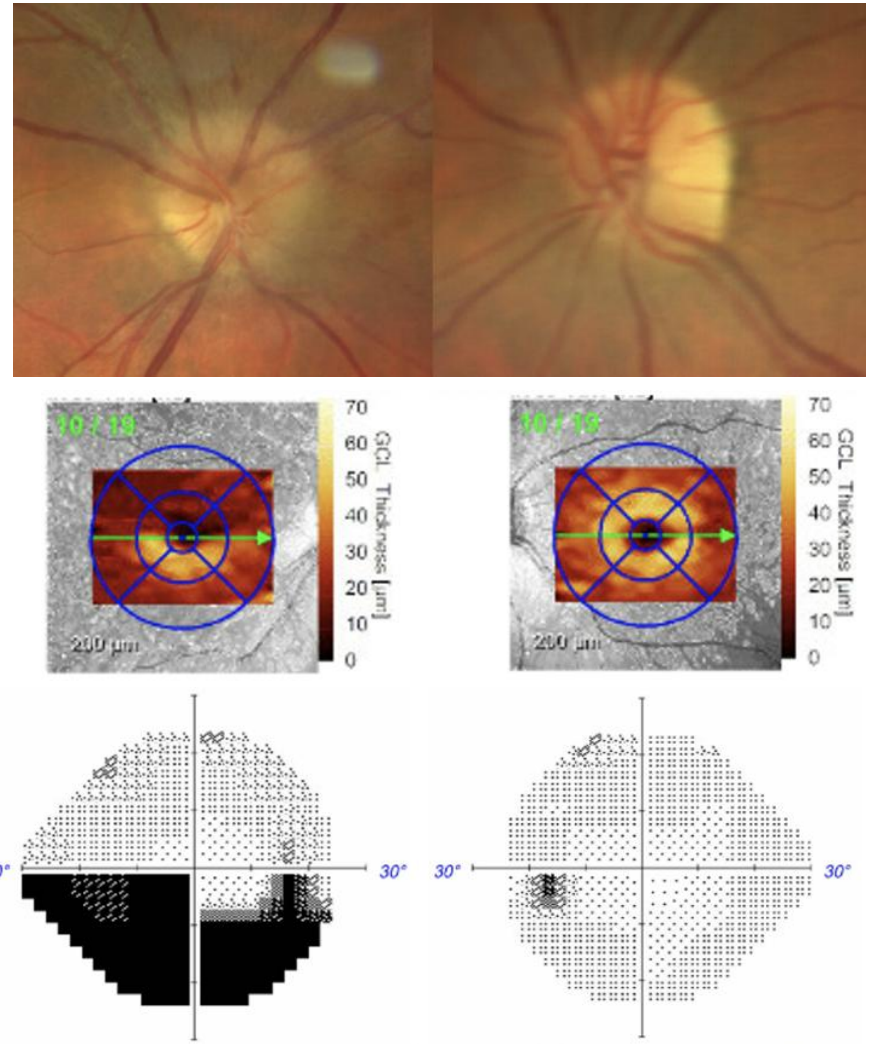
Is this optic neuritis? Something else?





Nonarteritic Anterior Ischemic Optic Neuropathy

	NAION
Age	▪ Usually >50yrs
Onset	▪ Sudden, often noticed upon awakening
Pain	▪ Usually painless
Optic disc	▪ Sectoral/diffuse edema, often hemorrhages; crowded disc fellow eye
Visual field	▪ Altitudinal defects common
MRI	▪ Usually no optic nerve enhancement



Miller NR, Arnold AC. Eye (Lond). 2015;29(1):65–79; Petzold A, *et al.* Lancet Neurol. 2022;21(12):1120–1134.

GLP-1 Receptor Agonists and NAION

What evidence suggests

- Semaglutide association with increased NAION risk in several observational studies
- Pooled estimates ~ 2x relative risk (absolute risk is low, 2-10/100k per year)
- EMA recognizes NAION as a very rare adverse effect of semaglutide

What remains uncertain

- Causality remains disputed, some large studies show no association
- Estimates vary substantially across studies
- Whether the risk extends to other GLP-1 receptor agonists

AAO/NANOS

- No routine ophthalmic screening solely before starting GLP-1 therapy
- If NAION develops, individualized shared decision-making about continuing or discontinuing treatment—not automatic discontinuation for every patient

Hathaway JT, *et al*. JAMA Ophthalmol. 2024;142(8):732–739; North American Neuro-Ophthalmology Society and American Academy of Ophthalmology. Ophthalmology. 2026;133(8):1029–1035; European Medicines Agency. PRAC safety communication on semaglutide and NAION. 2025.

Arteritic Anterior Ischemic Optic Neuropathy (AAION) and Giant Cell Arteritis (GCA)

Presentation	▪ Sudden, painless, often profound monocular visual loss; may become bilateral
Systemic symptoms	▪ New headache, scalp tenderness, jaw claudication, constitutional symptoms; may be absent (occult GCA)
Optic disc	▪ Pallid or chalky-white edema, sometimes w/ cotton-wool spots
Laboratory evaluation	▪ ESR, CRP, CBC with platelet count (can be normal)
Diagnostic confirmation	▪ TAB (gold standard); vascular U/S used if expertise available; can be negative (skip lesions)
Treatment	▪ Immediate high-dose steroids when strongly suspected—do not wait for diagnostic confirmation



Adapted from Chen et al., Front Med. 2022; Figure 1.

Hayreh SS, *et al.* Am J Ophthalmol. 1998;125(4):521–526.; Maz M, *et al.* Arthritis Rheumatol. 2021;73(8):1349–1365. Dejaco C, *et al.* Ann Rheum Dis. 2024;83(6):741–751; Chen Q, *et al.* Front Med (Lausanne). 2022;9:885463.

NAION vs AAION: Recognizing the Difference

	NAION	AAION (GCA-associated)
Age	▪ Usually >50yrs	▪ Usually >70yrs
Vision loss	▪ Sudden, painless; variable severity	▪ Sudden, painless; often profound
Optic disc	▪ Diffuse/sectoral edema, often hemorrhages	▪ Pallid, chalky-white edema
Systemic symptoms	▪ Usually absent	▪ HA, jaw claudication, scalp tenderness; may be absent
Inflammatory markers	▪ Usually normal	▪ ESR/CRP often elevated; occasionally normal
Management	▪ Optimize vascular risk factors; no proven vision-restoring therapy	▪ Immediate high-dose glucocorticoids

Miller NR, Arnold AC. Eye (Lond). 2015;29(1):65–79; Hayreh SS, *et al.* Am J Ophthalmol. 1998;125(4):509–520; Maz M, *et al.* Arthritis Rheumatol. 2021;73(8):1349–1365.

Hereditary Optic Neuropathies

Leber Hereditary Optic Neuropathy

- Onset: Adolescence, young adults
- Vision loss: Acute/subacute, often sequential bilateral
- Fundus: Early *pseudoedema,* peripapillary telangiectasias; later optic atrophy
- Genetics: Mitochondrial DNA



Dominant Optic Atrophy (OPA1)

- Onset: Childhood
- Vision loss: slowly progressive bilateral vision loss
- Fundus: Temporal optic disc pallor, often central/cecocentral field loss
- Genetics: Autosomal dominant



Adapted from O'Neill et al., Nat Rev Neurol. 2009; Figure 3,4.

Wolfram Syndrome (*WFS1*)

- Onset: Usually childhood or adolescence
- Vision loss: Progressive bilateral
- Fundus: Bilateral optic atrophy, no distinctive appearance
- Genetics: Classically AR, dominant can occur

Systemic association ("DIDMOAD"): DI, DM, deafness

Newman NJ, *et al*. Lancet Neurol. 2023;22(2):172–188; O'Neill EC, *et al*. Nat Rev Neurol. 2009;5:277–287; Barrett T, *et al*. GeneReviews®. Updated 2022.

Beyond the Eye: Optic Atrophy Can Signal Systemic Disease

Disorder	Key systemic manifestations
OPA1- DOA+	Hearing loss, peripheral neuropathy, ataxia, external ophthalmoplegia
WFS1- Wolfram syndrome	Diabetes mellitus, diabetes insipidus, hearing loss
LHON+	Movement disorders, ataxia, neuropathy, cardiac conduction abnormalities

Newman NJ, *et al.* Lancet Neurol. 2023;22(2):172–188; Yu-Wai-Man P, *et al.* Brain. 2010;133(3):771–786; Barrett T, *et al.* GeneReviews®. Updated 2022.

One Swollen Optic Disc, Multiple Diagnoses: A Practical Diagnostic Approach

Patient with suspected optic neuropathy

Visual acuity, color vision, rAPD, fundus exam, visual fields

Acute/subacute vision loss

- *Pain w/ EOMS ± normal disc:* MS-associated ON, AQP4-NMOSD
- *Pain w/ EOMs + marked disc edema:* MOGAD
- *Sudden, painless loss + disc edema:* NAION, AAION/GCA
- *Disc edema + macular star/subretinal fluid:* Neuroretinitis
- *Vitritis or CNS inflammation:* CRMP5, GFAP astrocytopathy

Chronic/progressive vision loss

- *Childhood-onset, slowly progressive bilateral loss: OPA1*-associated dominant optic atrophy
- *Optic atrophy + endocrine/auditory findings: WFS1*-associated disease
- *Unexplained progressive optic neuropathy:* Exclude compressive, infiltrative, toxic, nutritional causes
- *Remember the exception:* LHON often presents sub-acutely with sequential bilateral vision loss

Urgent exclusion: GCA

- Age ≥50 with acute ischemic optic neuropathy, particularly pallid disc edema: evaluate immediately

Bennett JL, *et al.* Lancet Neurol. 2023;22(1):89–100; Miller NR, Arnold AC. Eye (Lond). 2015;29(1):65–79; Newman NJ, *et al.* Lancet Neurol. 2023;22(2):172–188.

Beyond MS: Five Clinical Pearls to Take Home

1) Not every swollen optic disc represents optic neuritis

Consider neuroretinitis, ischemic optic neuropathy, and other inflammatory disorders

2) Recognize atypical optic neuritis

Bilateral involvement, marked disc edema, unusual MRI patterns, poor recovery should broaden the differential

3) The tempo of vision loss can help guides the diagnosis

Acute vision loss with disc swelling has different differential than subacute, slowly progressive bilateral

4) MOGAD and AQP4-NMOSD have different visual prognoses

MOGAD often has substantial recovery; AQP4-NMOSD carries greater risk of permanent visual disability

5) Never miss giant cell arteritis

Sudden visual loss in an older adult warrants urgent evaluation; treatment should not wait for biopsy

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Thank you

